

Functional Uterine Bleeding

Etiologic Factors and Therapy

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IT IS CONVENIENT to divide cases of excessive uterine bleeding into two general classes, those in which the cause of bleeding is readily ascribed to observable pathologic conditions, and those in which it is assumed to be from "functional" causes. A practical definition of functional uterine bleeding is bleeding that is not associated with neoplastic, inflammatory or trophoblastic change within the pelvis. Obviously, in such circumstances the cause is difficult to diagnose.

HISTORICAL SURVEY

Historically, the development of knowledge of the endometrial patterns associated with functional uterine hemorrhage presents a fascinating story. The recovery from the early misleading nomenclature was a masterful feat in itself, but the persistence of erroneous theories long after the true situation was established is rather dismaying. A brief historical sketch is necessary to an understanding of the confusing and mixed nomenclature associated with various descriptions of this subject.

With the introduction of the curette into gynecology by Recamier in 1850,¹⁹ endometrium was removed for study. Grossly the tissue had a "fungous" and "granulation-like" appearance, and although there was frequently little departure from what we now consider normal endometrium it was assumed that this "fungous" condition was the result of inflammation. In 1875 Olshausen¹⁸ reported a study of *Chronische Hyperplasierende Endometritis* (Endometritis Fungosa) and in 1879 Ruge²⁰ wrote on *Aetiologie und Anatomie der Endometritis* describing a glandular, interstitial and "mishform" type. These reports, as well as those by others such as Duncan⁵ in the English literature, served to perpetuate descriptions that emphasized inflammation—"endometritis fungosa," "endometritis polyposa," and "hemorrhagic endometritis." In 1882 Brenneche³ suggested that Olshausen's "endometritis fungosa" was not inflammatory change but true hyperplasia. He observed further that the endometrial changes were the result of ovarian abnormalities, and termed the condition "endometritis hyperplastica ovarialis." Despite Brenneche's postulates and the later bacterial confirmation of the noninflammatory

• *Endometrial hyperplasia and irregular shedding of the endometrium comprise the largest group of known causes of functional uterine bleeding.*

Most patients with functional uterine bleeding have a normal endometrial pattern.

In a series of patients with functional uterine bleeding, it was noted that 69.7 per cent of endometrial specimens reported as normal showed evidence of hyalinized tissue which included endometrial glands. Tissue of this type was noted in only 3.5 per cent of curetted specimens from patients without functional uterine bleeding.

Diagnostic uterine curettage is the initial step in the management of functional uterine bleeding.

Hysterectomy and radiation castration are seldom necessary in the management of functional uterine bleeding and are indicated only under specific circumstances.

nature of the endometrium, and despite the acceptance of these observations by such authorities as Shauta and Cullen, the previous view persisted.

It was not until 1908, when Hitschmann and Adler⁸ from Shauta's clinic in Vienna published their classic work on normal cyclic changes in the endometrium, that it became apparent that so many of the previously described conditions were not inflammatory processes. Their article was beautifully illustrated and accompanied by classic descriptions of each phase of the cycle. Not long afterward (1912) Schröder²² published his fundamental investigations on the relationship of the endometrial cycle to the ovarian cycle. He also described in detail the entity of cystic glandular hyperplasia of the endometrium and correlated it with specific changes in the ovary.²³ Indeed, it was he who suggested²⁴ the term "metropathia hemorrhagica" for this condition. It was at this point that the present concept of the ovarian-endometrial cycle and the nature of endometrial hyperplasia became firmly established. Since that time the less frequent causes of functional uterine bleeding have been described and explained with varying degrees of successful acceptance.

Numerous references to and descriptions of delayed or irregular shedding of the endometrium^{1, 4, 12}

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were made before Meyer¹⁷ described the entity so completely in 1930. In the American literature Traut and Kuder (1935)²⁷ described irregular shedding and irregular ripening of the endometrium and stated that these disorders were the etiologic factors in one-third of the cases of functional bleeding observed by them. Later McKelvey (1942, 1947)^{13, 14} and Holmstrom and McClennan (1947)⁹ firmly established the verity of irregular endometrial shedding with the publication of their carefully selected studies. According to Traut, irregular ripening is characterized by intermenstrual bleeding associated with a condition of patchy distribution of both secretory and nonsecretory endometrium. Irregular or delayed shedding of the endometrium is characterized by prolonged (seven or more days) and often excessive cyclic uterine bleeding associated with the persistence or retention of secretory endometrium five or more days following the onset of menstruation. As opposed to endometrial hyperplasia it has no predominance in the menarche or climacteric. Holmstrom and McClennan were able to produce this clinical picture by administering progesterone during the bleeding phase of the menstrual cycle. McClennan (1952),¹⁶ reporting the largest series to date, emphasized the effectiveness of curettage in therapy.

As to the causes of uterine bleeding considered "functional" in nature, only bleeding associated with endometrial hyperplasia and delayed endometrial shedding has been satisfactorily explained. Holmstrom and McClennan expressed mild skepticism concerning irregular ripening as a substantial cause of metrorrhagia. The following is a list of the endometrial conditions which have been observed in careful histologic studies of curetted endometrium associated with functional uterine bleeding:

1. Endometrial hyperplasia
2. Delayed endometrial shedding
3. Irregular endometrial ripening
4. Normal endometrium (a) secretory endometrium, (b) proliferative endometrium, (c) menstruating endometrium.

The reported proportions of the various types of endometrium have varied from study to study. Endometrial hyperplasia has been reported in from 23 to 68 per cent of cases, with most observers reporting a 30 to 40 per cent incidence.²⁶ The reported incidence of nonhyperplastic endometrium has varied from 30 to 70 per cent, with delayed shedding making up 7 to 15 per cent of this group. Recently Sutherland²⁵ in two masterful surveys of "functional" uterine bleeding compared the type of endometrium in 1,000 patients without "organic" pelvic lesions with the type in 1,000 patients with gross anatomic defects (Table 1). The proportions of the endometrial types in the two groups were remarkably similar. Unfor-

TABLE 1.—Condition of endometrium of 1,000 patients without organic lesions, as compared with condition in 1,000 patients who had gross anatomic defects (after Sutherland²⁵)

Endometrium	Patients without Organic Lesions	Patients with Anatomic Defects
Normal	547	648
Hyperplasia	265	195
Irregular Shedding and Ripening.....	39	18
Others (non-functional)	149	139
Total	1000	1000

tunately, in the largest group of patients, those with normal endometrium, the mechanism or cause of bleeding has been poorly explained. Certainly it is agreed that abnormal bleeding may arise from any type of endometrium, secretory included.¹¹ This situation has led to undue emphasis of such explanations of bleeding as nutritional deficiencies (vitamin B complex),² low thyroid function,⁷ increased capillary fragility (vitamin P),⁶ and increased plasma protamine titrations.²⁰ These explanations, in the authors' experience, apply to only a small percentage of this large group of functional bleeders.

ANALYSIS OF MATERIAL

In a retrospective study, the records of patients with functional uterine bleeding observed in the gynecologic clinic in a 3-year period 1950-1953 were reviewed. The clinical courses were carefully considered to establish the condition of abnormal uterine bleeding, and then all cases in which there was a pelvic neoplasm, pregnancy effect, pelvic inflammatory condition, or non-neoplastic pelvic tumor (such as adenomyosis or endometriosis) were excluded from the study. In all, the series included 235 women and, as initially considered, the types of endometrium encountered were:

	Number	Per cent
Endometrial hyperplasia.....	50	21
Proliferative endometrium.....	103	44
Secretory endometrium.....	64	27
Menstrual endometrium.....	18	8
Total	235	100

It was noted that in 79 per cent of cases there was no anatomical diagnosis to account for the abnormal bleeding. It must be emphasized that, during this period, a concerted effort was not always made to time the curettage in order to obtain the maximum chance of demonstrating the diagnosis histologically. While this timing was always desired it was often impractical and, occasionally, impossible. In spite of the inopportune timing of the curettage, the small percentage of definitive diagnoses led the authors to consider the normal endometria in more detail.

In reviewing the clinical records and histological specimens, it was possible to diagnose delayed endometrial shedding in 23 patients (Figure 1). These were patients in the proliferative endometrium

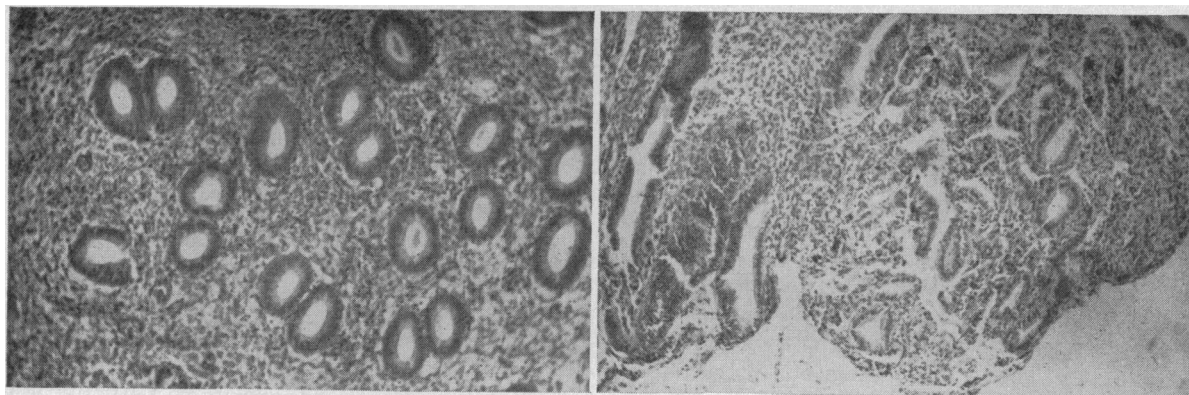


Figure 1.—Irregular endometrial shedding. Note normal proliferative endometrium (seventh day of cycle) on the left and collapsed secretory glands on the right.

TABLE 2.—Association of endometrial abnormalities in 235 cases of functional uterine bleeding abnormality and normality of endometrium.

	Normal endometrium	Abnormal endometrium	
Endometrial hyperplasia.....		50	} 31%
Irregular shedding		23	
Proliferative endometrium			
Normal	21		} 48%
With hyalinized tissue		59	
Secretory endometrium			
Normal	21	43	
With hyalinized tissue.....			
Menstruating endometrium			
Normal	8		} 10
With hyalinized tissue.....		10	
	50 (21%)	185 (79%)	

group, who had noted a prolongation and/or increase in cyclic menstrual flow, in whom retention of late secretory endometrium was confirmed on the fifth to seventeenth day after the onset of menstruation. Normally the secretory endometrium should have been shed by at least the third day of menstruation. Often the retained secretory endometrium was degenerating and was surrounded by varying amounts of a hyalinized type of tissue (Figure 2). In this respect it is noteworthy that a large number of specimens in the normal endometrium group also showed this hyalinized tissue. The hyalinized tissue usually contained, or surrounded in intimate association, degenerating endometrial glands and was infiltrated by varying numbers of fibroblasts (Figure 3). Characteristically, no inflammatory reaction was present. Table 2 indicates the number of cases in which this endometrial pattern was associated with the 235 cases of functional uterine bleeding.

It was noted that hyalinized tissue of this kind was found in the curettings from functional bleeders in both proliferative and secretory phases of the menstrual cycle. The addition of these cases to the others with abnormal endometrium makes it possible to associate the abnormal bleeding with an anatomically demonstrable factor in 79 per cent of the pa-

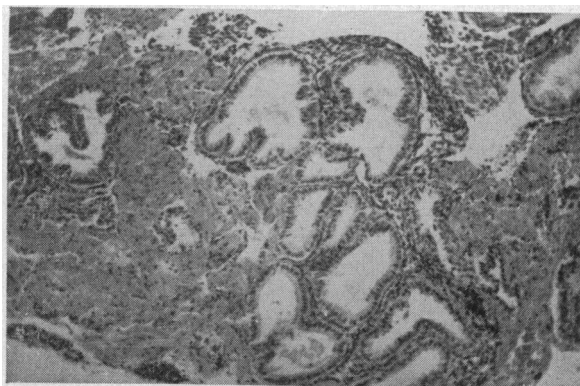


Figure 2.—Irregular endometrial shedding. Note the retained secretory endometrium intimately surrounded by hyalinized tissue.

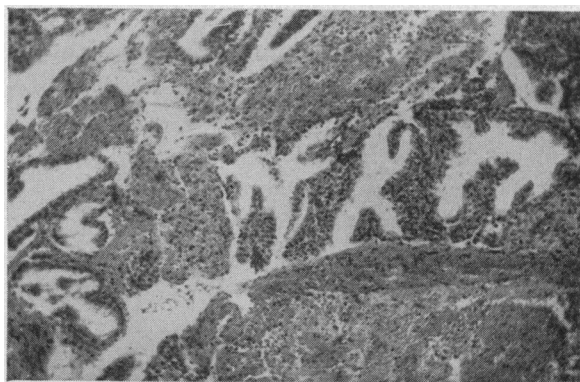


Figure 3.—Hyalinized substance surrounding endometrial glands. The hyalinized material is extensively infiltrated by fibroblasts.

tients. It was frequently possible to identify the glands contained within the hyalinized substance as either proliferative or secretory. When such retained secretory endometrium was found in association with proliferative endometrium (Figure 4), it suggested delayed or irregular shedding of the endometrium. However, it must be emphasized that such conclusions are warranted only when the clinical restrictions ascribed to irregular shedding of the endo-

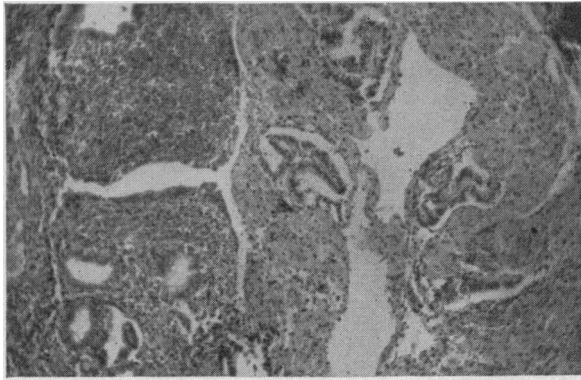


Figure 4.—Secretory glands included within hyalinized substance. Note proliferative endometrium on the right.

metrium have been satisfied. The authors prefer to call it retained, hyalinized endometrial tissue.

How often is this hyalinized tissue observed in the absence of abnormal uterine bleeding? To answer this question, the tissues curetted during the same period from patients who were menstruating normally were reviewed. In large part the patients had had curettement routinely at the time of a vaginal plastic procedure. The following findings were noted:

	No. cases	Per cent
Normal secretory endometrium.....	12	93
Normal proliferative endometrium.....	12	
Proliferative endometrium with hyalinized tissue	1	3.5
Endometrial hyperplasia.....	1	3.5
Total	26	100

Thus, a high incidence of the phenomenon of hyalinized tissue retention was noted in association with abnormal bleeding and a low incidence in normally menstruating women. It is possible that endometrial glands retained through the bleeding phase of menstruation might continue as a stimulant for further bleeding. Blood surrounding these accumulations could organize to form just such a histologic structure as that described. This tissue, once organized and firmly attached, might serve as a focus of continued bleeding. It is equally possible that any bleeding, including that associated with menstruation, might result in clotted blood becoming organized and eventually bring about the phenomenon. When degenerated glands within hyalinized tissue are observed, especially early in the menstrual cycle, there is strong suggestion they were retained from a previous cycle. This picture of hyalinization and retention is noted here only insofar as it supports evidence of previous abnormal bleeding and possibly the abnormal retention of endometrial elements. Of academic importance is the possibility that retained hyalinized fragments, with included endometrium, account for bleeding in a substantial number of patients with functional uterine bleeding. With this a possibility, there is further justification

for uterine curettage as a logical therapeutic measure in such cases.

DISCUSSION

Quite naturally the management of abnormal uterine bleeding will vary with the age and parity of the patient, especially if the bleeding is designated as functional. A practical scheme of management is to consider the following measures in order:

1. *Uterine Curettage.* A sound principle in the management of undiagnosed menometrorrhagia is to be as radical as necessary to make sure malignant disease is not present and, after a benign cause has been established, to be as conservative as possible in the treatment. As an initial measure, thorough curettage is usually best for the following reasons: It eliminates or establishes malignancy as a cause; it establishes the diagnosis on a sound basis; it is the most effective method of stopping the bleeding initially; and it is associated with cure in approximately 50 per cent of cases of functional bleeding.

It is prudent, of course, to follow McClennan's advice (1951)¹⁵ and carry out curettage at the best time for establishing the diagnosis histologically. It cannot be too strongly emphasized that curettage, not hysterectomy, is the initial definitive measure in the diagnosis and treatment of abnormal uterine bleeding.

2. *Diet and General Measures.* Experimentally and clinically the Biskinds and others have noted the value of dietary measures in functional uterine bleeding. The fact that vitamin B complex is necessary for the proper metabolism of estrogens in experimental animals cannot be directly applied to clinical therapy but it is logical to treat any associated systemic disease or dietary deficiency. However, such conditions have been observed by the authors in relatively few patients.

3. *Cyclic Steroid Hormone Therapy.* Curettage is vastly superior to large repeated doses of estrogens in the initial suppression of alarming uterine bleeding. If the patient does not respond to curettage, cyclic suppression and release of gonadotrophic activity by estrogen administration is then in order. Stilbestrol by mouth for 21 days, then a seven-day period in which the hormone is not given constitutes the cycle. The dose of 0.5 mg. to 3.0 mg. per day may be increased from the first to the third week, and in the authors' experience stilbestrol is as effective and as well tolerated as the more expensive estrone sulfate or estradiol. In order to luteinize the endometrium and perhaps bring about a more physiological type of withdrawal bleeding, 25 mg. of progesterone may be given orally each day during the third week of the cycle of hormonal treatment, or, if convenient, 1 cc. of progesterone (50 mg. in aqueous suspension) may be given intramuscularly on the twenty-first day. In controlling bleeding asso-

ciated with anovulatory cycles, Holmstrom¹⁰ used only a 25 mg. injection of progesterone each month, thereby eliminating the use of estrogens in a condition felt to be caused by an excess of estrogens. By and large, the reasoning behind the use of cyclic steroid therapy is logical; and clinically the treatment is often effective. Perhaps a valuable feature of the therapy described is that it allows the passage of time in a disease which is usually self-limited.

4. *Androgen Therapy* in functional uterine bleeding is rational only in controlling the initial phase of bleeding. The disadvantages (i.e., masculinization) of its continued use are disconcerting and the method does not seem physiologically sound.

5. *Hysterectomy*. This is a radical method of treating functional uterine bleeding. It is indicated only in women less than 45 years of age when an adequate trial of more conservative measures has proved ineffective. For patients under the age of 35 this procedure is seldom necessary and should be considered with grave concern. This hesitancy is justified in the younger age group not only from the standpoint that hysterectomy is seldom necessary but also because the procedure interrupts a substantial portion of the ovarian blood supply. Also, sudden cessation of menses in a young woman may have more profound effects than are usually anticipated.

6. *Radiation Castration*. This is also a radical method of treating uterine bleeding of benign cause and has been increasingly criticized as operative procedures have become safer and more widely used. However, it does have a place. The use of 1500 r of pelvic x-radiation, or 1500 mg. hours of intrauterine radium is usually sufficient for the purpose and is definitely indicated, in functional uterine bleeding, for patients over 45 years of age in whom adequate conservative measures have proved ineffective. It is best that these age figures be regarded as physiologic estimates rather than as chronologic. In this way a logical flexibility may be exercised. Radiation castration is also indicated as a last resort in the case of younger patients whose general condition contraindicates major operation.

The problem of managing functional uterine bleeding is somewhat simplified by the consideration of two observations: (1) Curettage alone cures functional bleeding in approximately 50 per cent of cases; (2) the majority of cases occur during the menarche or the climacteric, periods which in themselves are temporally limited and consequently act as self-limiting effects. This knowledge encourages temporization with the employment of conservative measures. Such measures discourage the use of irreversible radical procedures while the body is making the necessary adjustments to correct the abnormal bleeding.

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